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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/546,857	04/10/2000	Brian C. Cunningham	P1734R1	3105

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EXAMINER

SPECTOR, LORRAINE

ART UNIT PAPER NUMBER

1647

DATE MAILED: 08/20/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n N .

09/546,857

Applicant(s)

CUNNINGHAM ET AL.

Examiner

Lorraine Spector, Ph.D.

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P r i d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 May 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

- 4) ☒ Claim(s) 20-54 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 20-54 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 April 2000 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachm nt(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

Part III: Detailed Office Action

Species Election Requirement:

The species election requirement is withdrawn. Claims 20-54 are pending and under consideration.

Formal Matters:

The abstract of the disclosure is objected to it should indicate that the VEGF mutants of the invention have substitutions at one or more of positions 17-25 and 63-66. Correction is required. See MPEP § 608.01(b).

The drawings are objected to the copy quality of Figure 15A is not sufficient; no information can be gained from the figure. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim 54 is objected to under 37 CFR 1.75(c), as being of improper dependent form for depending from two other claims inclusively. A dependent claim may depend from multiple other claims in the alternative only. Further, the claim depends from cancelled claim 6. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 28, 29 and 48 are objected to because of the following informalities: In claims 28, 29 and 48, the word "comprises" should read ~~comprise~~. Appropriate correction is required.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5 Claims 20-54 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10 All claims are indefinite for failing to point out that it is variants of *human* VEGF that are the subject of the invention. The residue numbers recited in the claims apparently relate to the human VEGF sequence, and as the residues differ among species, the claims are indefinite as they relate to non-human forms of VEGF. As this application contains no sequence disclosure but relies upon the accepted numbering of human VEGF, it is essential that the protein of reference, human VEGF, be specified in the claims.

15 All claims with the limitation that "the amino acid substitutions increase the relative binding affinity ratio of KDR to FLT-1" are indefinite, as KDR does not bind to FLT-1. The binding ratio that is being altered is the ratio of *VEGF binding* to the KDR and FLT-1 receptors.

20 Claims 45 and 46 are incomplete as they fail to adequately identify the cells to be used; the claims merely specify that the cells express KDR; only appropriate cells that express KDR will be effective for the stimulation of vasculogenesis or angiogenesis; similarly, only endothelial cells expressing KDR will meet the limitations of claim 46. Further, contacting a single cell with VEGF would be unlikely to stimulate either vasculogenesis or angiogenesis; amendment of claim 45 to the plural "cells" is suggested.

25 Claim 54 depends from a cancelled claim, and is therefore indefinite. For purposes of compact prosecution, the claim will be interpreted as though it read "An isolated nucleic acid encoding the VEGF variant of claim 50".

All remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

5 (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

10 (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

15
20 This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

25 Claim(s) 23, 32, 36-44, 46, 47 and 53 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Fuh et al., JBC 273(18):11197-11204, cited by applicants.

30 Claim(s) 23, 32, 36-44, 46, 47 and 53 are drawn to muteins of VEGF having substitutions at one or more of positions 17-25 and one or more of positions 63-66, and which have a property of having an increased binding affinity for KDR relative to Flt-1. Fuh et al. teach a VEGF variant having substitutions C60S, F17A, E64A, see page 11198, first column, which is consistent with the

structural limitations of the claims. Fuh et al. are silent with respect to the relative binding affinity of the mutein for KDR as relative to Flt-1. The examiner is unable to determine whether the prior art disclosure possesses the unrecited characteristics or property. However, in view of the teachings of Keyt et al, U.S. Patent Number 6,020,473, it appears probable that the mutein had an increased binding affinity for KDR as compared to FLT-1. Under such circumstances, where the product seems to be identical except that the prior art is silent to the characteristic or property claimed, then the burden shifts to applicant to provide evidence that the prior art would neither anticipate nor render obvious the claimed invention. Note the case law of *In re Best* 195 USPQ 430, 433 (CCPA 1977).

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Muller et al., Structure 6:1153-1167, 1998, disclose VEGF with substitutions Phe17Ala and Tyr21Ala. Both showed increased IC_{50} values for binding to anti-VEGF antibody relative to wild-type. Binding to KDR and Flt-1 was not assessed.

Muller et al., et al., PNAS 94:7192-7197, cited by applicants, disclose alanine scanning mutagenesis of VEGF, with assessment of relative affinity of the mutants for KDR. Mutations were made at each of positions 17-25 and 63-66, with varying results on KDR affinity compared to wild type. There is no suggestion of a differential in binding to KDR and Flt-1, nor is there any suggestion to mutate at *both* regions 17-25 and 63-66.

Siemeister et al., JBC 273(18):11115-11150, 1998, disclose that VEGF muteins with serine residues substituted at positions 14, 15, 17 and 18 failed to form biologically active dimers.

U.S. Patent Number 6,020,473 discloses VEGF muteins having alanine-residues substituted at positions 63 and 66. At column 34, they disclose that there is a minor KDR binding determinant site at positions 63-67, and that a D63A, E64A, E67A mutein was three fold reduced in binding to KDR. They further state at column 35 that the 63-67 region is a major determinant of FLT-1 binding. They disclose that the D63A, E64A, E67A mutein had 20-fold decreased binding to FLT-1;

thus, they disclose a mutant of VEGF that has an increased relative binding affinity for KDR as compared to FLT-1. There is no suggestion to make substitutions at residues 17-25, nor specific substitutions of serine at position 63 nor arginine at position 66.

Weintraub et al, U.S. Patent Application Publication Number US2002/0169292A1, disclose
5 a variety of VEGF muteins including substitutions at positions 17-25 and 63-66, see paragraph [0537]. There is no suggestion to combine substitutions at those two regions.

Advisory Information:

No claim is allowed.

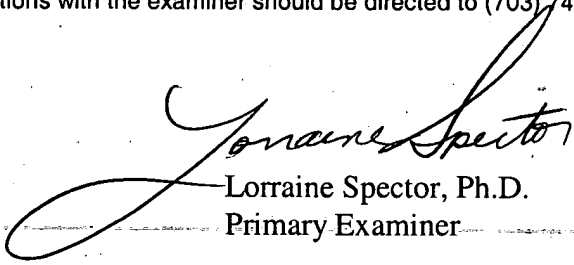
10 Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M.

15 If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

20 Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED
25 so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228.

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Lorraine Spector, Ph.D.
Primary Examiner

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8/6/03